



## Adverse Changes in the Cardiovascular System Observed when using a Combination of Antihypertensive Drugs

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**Annotation:** The analysis of literary data on clinical efficacy and safety of antihypertensive medicines indicates the significant difference between the original and generic medicines both on therapeutic equivalence and on the frequency and intensity of the expressiveness of adverse side reactions, caused by them.

**Key words:** hypertension, antihypertensive medicines, the original preparation, generic drug, therapeutic equivalence, adverse side effects.

Arterial hypertension (AH) is a prolonged increase in blood pressure (BP) over 140/90 mm Hg. (systolic blood pressure and diastolic blood pressure, respectively) in individuals not receiving adequate antihypertensive therapy.

AH is one of the leading risk factors for the development of cardiovascular and cerebrovascular diseases, which are the main cause of high mortality and disability population in all countries, and the most common cardiac pathology. The prevalence of hypertension is high worldwide, 20-30% of the adult population in developed countries suffer from hypertension. [1,4]

In Uzbekistan, AH occurs in 30-40% of the adult population, and in individuals older than 60 years is much more common - up to 60-70%. The main types of hypertension are essential hypertension or hypertension, the etiology of which is unknown, it accounts for 90-95% of patients with hypertension, and secondary hypertension is symptomatic, the cause of which may be kidney pathology (lesion renal parenchyma), adrenal glands (pheochromocytoma, hyperaldosteronism), large vessels (renal artery stenosis, aortic coarctation). There is also an isolated systolic hypertension, in which systolic blood pressure exceeds 160, and diastolic blood pressure is less than 90 mm Hg. This form Hypertension occurs mainly in the elderly and is caused by a decrease in vascular elasticity.

Adequate treatment of hypertension should lead to a decrease in pressure to the so-called target values (140/90 mm Hg, with diabetes and kidney pathology - 130/80). The prognosis for hypertension depends not only on the value of blood pressure. Of great importance are: the presence of concomitant risk factors: age, family history of early cardiovascular disease, smoking, high cholesterol and violation of the lipid spectrum of blood plasma, hypodynamia; weight gain; abdominal obesity, diabetes mellitus (DM), large doses of alcohol; degree target organ damage and the presence of associated clinical conditions [5,8].

The main goal of hypertension treatment is to reduce mortality from cardiovascular diseases. Strategy Antihypertensive therapy is being developed to prevent end-organ damage and mortality associated with elevated blood pressure levels. Highest risk of myocardial infarction or cerebral stroke in patients with high levels of blood pressure occurs precisely when stopping (even temporarily) antihypertensive therapy. According to a meta-analysis of numerous clinical studies, a decrease in systolic BP by 12-13% leads to a decrease in cardiovascular complications by 21-37%. Adequate, regular antihypertensive therapy leads to a decrease in mortality patients: from myocardial infarction - by 15-20%, from cerebral stroke - by 40-50%. This explains the need for timely and rational treatment [6,8].

According to the world's leading experts, the treatment of hypertension should be as early and intense as possible. Therefore, a combination of two or more antihypertensive drugs is often required for effective treatment, even in the early stages of the disease. In combination therapy, lower doses of drugs are used, which reduces the risk of side effects; there is a simultaneous effect on different mechanisms of hypertension, which increases the effectiveness of treatment; in addition, fixed combinations of two or more drugs allow combination therapy with a single tablet, which more comfortable for the patient [7,8]. The main groups of drugs for the treatment of hypertension:

First-line drugs (basic): inhibitors angiotensin-converting enzyme (ACE); beta-blockers (BAB); Ca-channel blockers (Ca antagonists); diuretics; angiotensin receptor blockers (BAT1., sartans);

Second-line (alternative) drugs: alpha-blockers;  $\alpha$ 2-adrenergic and imidazoline receptor agonists (neurotropic central action, central sympatholytics), direct renin inhibitors.

Properties of the main groups of antihypertensive funds ACE inhibitors: more effective in young people; improve the quality of life; organoprotective action (cardio-, nephro-vasoprotective); prevent the progression of diabetic nephropathy; slow development addiction; positive metabolic effects: improvement of glucose metabolism, increased sensitivity of peripheral tissues to insulin, no effect on lipid metabolism, urea, creatinine levels; no withdrawal syndrome; but! can cause cough in 11.5% cases - on captopril, in 24.7% of cases - on enalapril as a result of irritation of the afferent fibers of the vagus nerve of the upper respiratory tract with bradykinin due to disorders of its metabolism, can increase the level of potassium blood and cause kidney failure; expensive.[4,6].

Beta-blockers (BAB): their effectiveness in BP is high, especially in young people; they reduce mortality from coronary heart disease in non-smokers; reduce the incidence of coronary heart disease and the rate of its progression; reduce mortality from myocardial infarction; but! may lower lipoprotein levels high density; cause sexual dysfunction in men; possible negative effect on cognitive function (lipophilic BAB); peripheral vasoconstriction, bronchospasm (non-selective BAB); high doses - bradycardia and heart failure. Give withdrawal syndrome. There are cheap drugs (propranolol).

Thiazide diuretics: currently diuretics occupy one of the leading positions among modern means for long-term treatment of hypertension; more effective at elderly patients; reduce the risk of stroke in smokers and non-smokers; delay the excretion of calcium and prevent pathological fractures in osteoporosis; large doses (dichlothiazide above 25 mg) can reduce plasma potassium, cause impotence, increase total cholesterol and low-density lipoprotein cholesterol, glucose and urea, therefore, are not indicated for hypokalemia, patients with diabetes mellitus, gout; important: low doses of hydrochlorothiazide and thiazide-like diuretics, used to treat hypertension (hydrochlorothiazide 12.5-25 mg), have a satisfactory safety profile, not have a clinically significant effect on carbohydrate, lipid and purine and electrolyte metabolism and well tolerated by patients, which allows for long-term therapy. Indapamide, unlike other thiazide and thiazide-like diuretics has a minimal effect on the content of potassium and uric acid, almost does not change the plasma concentration of glucose and does not impair the sensitivity of peripheral tissues to the action insulin, therefore it is the safest for the treatment of arterial hypertension in patients with diabetes mellitus, has

slight diuretic effect. Diuretics are good combined with ACE inhibitors, BAB, BAT1. The drugs are inexpensive.

Ca-channel blockers: very effective in treating hypertension, especially in the elderly; effective in coronary heart disease, but with post infarction cardio sclerosis are practically useless; their advantages - reduce systolic blood pressure and diastolic blood pressure without causing orthostatic hypotension; metabolically neutral - do not affect the lipid profile, carbohydrate, purine metabolism, electrolyte balance); have antiaggregatory activity; have a cardio protective effect (more pronounced verapamil and diltiazem); possible adverse effects associated with vasodilation - headache, dizziness, flushing, palpitations, transient hypotension, peripheral edema of the feet, ankles, elbows - more characteristic of short-acting nifedipine; bradycardia, rare events of heart failure (verapamil).

When prescribing drugs, the following main factors should be taken into account: the effectiveness of drugs, the effect on quality of life, metabolism, drug cost and its pharmacoeconomic and qualitative characteristics, and, in this connection, its origin is very important, i.e. original this drug or reproduced (generic).

Generic (generic) drug - a generic drug that is interchangeable with its patented analogue (original drug) and brought to the market at the end of the patent protection of the original. Distinctive characteristics generic drugs: copying the original drug, because the patentee submits an incomplete dossier on the original; low indicators of quality, efficiency and safety; appearance on the market after the expiration of the patent protection of the original drug; lack of preclinical and clinical studies; as a rule, uninformative instruction; allowed for circulation based on the assessment of the registration dossier reduced volume and bioequivalence data; production is not always carried out according to GMP rules; low cost per package. Generic drugs produced by pharmaceutical companies in countries Eastern Europe, Asia, Latin America, CIS, including RF. There are several tens of thousands of generic drug manufacturers around the world, they operate in completely different economic and regulatory conditions.

Therefore, often the "cheapness" of a generic turns out to be even more additional expenses for the patient for the use of a larger dosage of an ineffective generic drug, treatment of unwanted side effects and compensation for a more severe clinical condition [2]. So in a randomized study compared the effectiveness of several generics of Enalapril (Enapa, Ednita, Invoril, Envas and Enam) with the original drug Renitec and showed that doses may be required to achieve the effect of some of them, exceeding the doses of the original drug by almost 3 times. In addition, pharmacoeconomic studies of enalapril preparations have shown that a course of treatment, for example, with the "cheap" Enap is much more expensive than treatment with the original drug Renitec [5].

When studying the efficacy and safety of generics Indapamide showed a tendency to increase blood pressure by during the first 6-7 hours and 17-19 hours after them application, lack of normalization of the circadian rhythm of blood pressure and a pronounced negative effect on electrolyte metabolism, which is not typical for the original Indapamide [3]. At comparison of the original drug Bisoprolol with one of the its generics in patients with arterial hypertension 1-2<sup>nd</sup> degree, it was found that the generic significantly reduces systolic and diastolic blood pressure, however this decrease is significantly less pronounced (by 3-4 mm Hg), than lowering blood pressure under the action of the original drug. At first glance, such drugs can be interpreted as therapeutically equivalent, but with blood pressure, the frequency of achieving the target blood pressure values when using of the original drug was more than 20% higher than such when using a generic drug [6].

A comparative study of the original drug amlodipine (Norvasca) and one of the many generics of this drug – Cardilopin in patients with mild to moderate hypertension using a randomized, dual blind method showed that statistically significant differences in the severity of the hypotensive effect both

drugs were not identified, but there was only slight downward trend diastolic blood pressure 6 weeks after the start of treatment with Norvasc. Those. Cardilopin is the only fully studied generic, for other generics of amlodipine direct no comparisons of therapeutic equivalence with the original drug have been made [1,4].

So When choosing a drug, there are two questions:

- 1) What to prescribe - the original drug or generic?
- 2) If a choice is made in favor of a generic - which manufacturer do you prefer?

If there is a financial opportunity to buy the original drug It's better to buy the original. If there is a choice between several generics, it is better to buy a drug from a reliable manufacturer.

In the future, in the pharmacotherapy of complex diseases of the cardiovascular system, including hypertension, leading positions will be occupied by the original drugs. The best option for generics is generics manufactured in Eastern Europe, because these are mainly modern drugs, whose patent protection expired no more than 5 years ago. Generics Russian and Asian production, as a rule, are morally obsolete, tk. term of the patent their protection expired 10-15 years ago.

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